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REVIEW ARTICLE

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History and emerging trends in chemotherapy for gastric cancer

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Abstract

Chemotherapy is indispensable for gastric cancer. For unresectable and/or recurrent gastric cancer, first-line chemotherapy consists of multidrug regimens including oral 5-FU agents such as S1/Xeloda and platinum preparations, as well as Trastuzumab, which is effective in HER2-positive cases. Second- and third-line chemotherapy regimens include taxanes, Ramucirumab (R-mab), and Nivolumab (N-mab), which have different mechanisms of action from first-line chemotherapy. R-mab is molecularly targeted to vascular endothelial growth factor receptor 2 in the host cells, but its indication is not conditional. For resectable gastric cancer, in Eastern countries, postoperative adjuvant chemotherapy has been successful, including S1, Docetaxel/S1 (DS), and Xeloda/Oxaliplatin (Xelox) regimens, whereas, in Western countries, the 5-FU/Leucovorin/Oxaliplatin/Docetaxel (FLOT) regimen was recently shown to be effective in the perioperative chemotherapy setting. Most recently, however, in Eastern countries, perioperative SOX was demonstrated to be effective in specific advanced gastric cancer. For stage IV gastric cancer, new therapeutic strategies have been proposed such as neoadjuvant chemotherapy and conversion surgery, and cures can be conditionally obtained. Recent genomic understanding of gastric cancer proposed a diversity of molecular targets by molecular profiling. Such optimized chemotherapy regimens, according to the specific clinical situations, have been rigorously established for the best survival of advanced gastric cancer.

KEYWORDS

chemotherapy, resectable gastric cancer, stage IV, unresectable gastric cancer

1 | INTRODUCTION

Gastric cancer is increasing worldwide and is the second leading cause of death among human cancers.[1] Early gastric cancer showed excellent prognosis following surgery alone,[2,3] whereas advanced gastric cancer exhibits poor prognosis with surgery alone in Western countries[4,5] (overall survival [5-year OS] 20%-30%, Figure 1A,B) and in Eastern countries[6,7] (5-year OS 60%-70%, Figure 1C,D).

The different prognoses between Western and Eastern countries may be due to a different composition of advanced disease (the former included a curative rate of 66% following surgery,[4] whereas

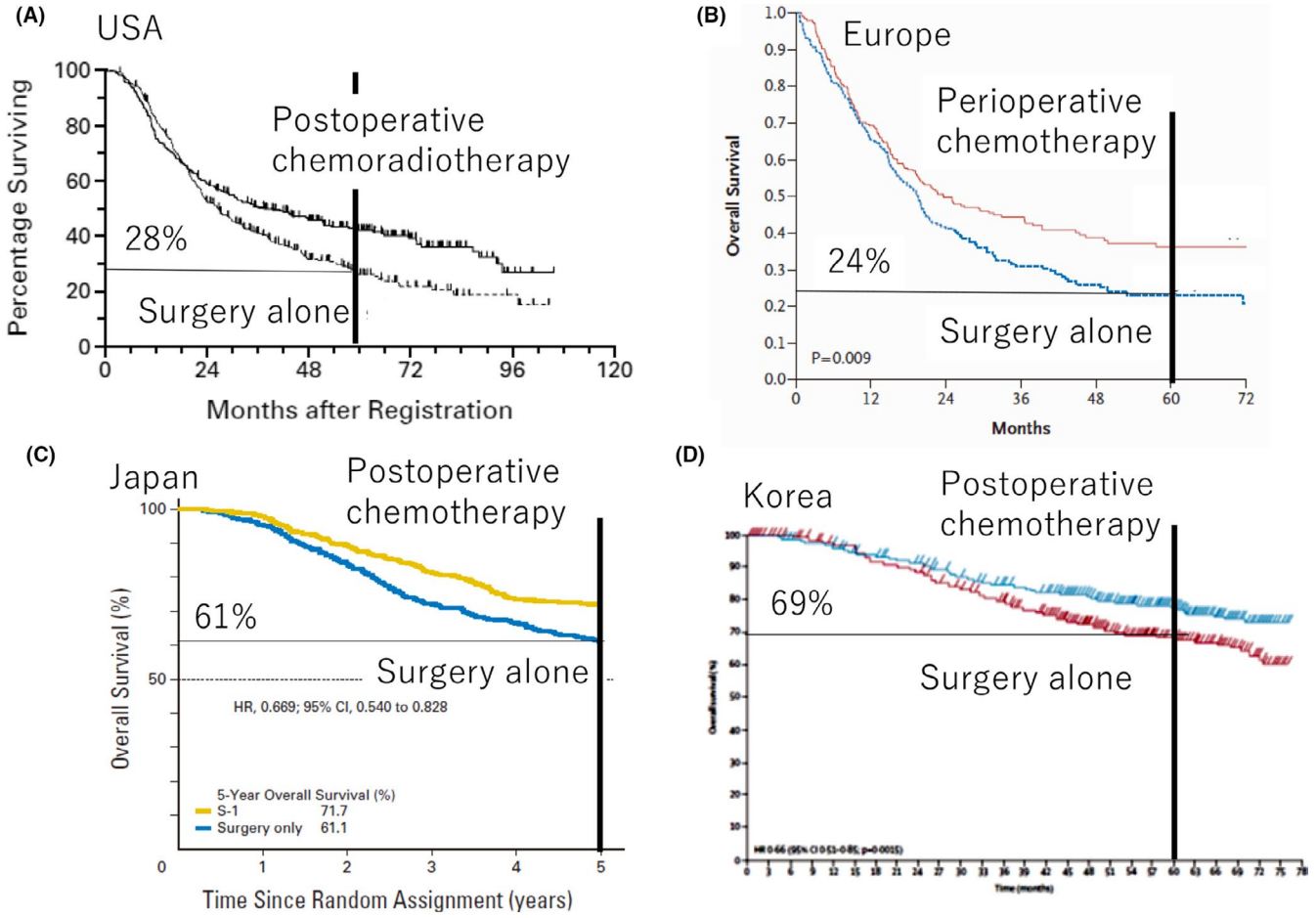
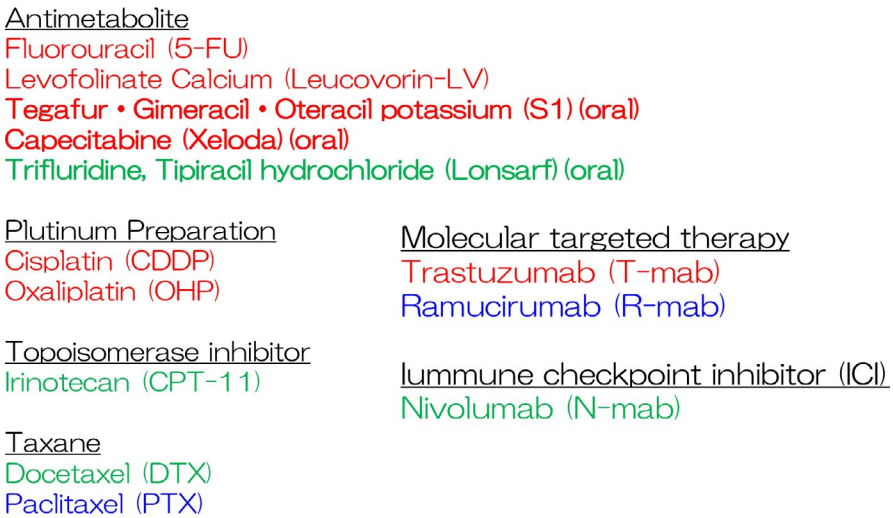


FIGURE 1 Overall survival (OS) in resectable advanced gastric cancer following surgery alone in phase III clinical trials. A, 5-year OS in the United States of America was 27% following surgery alone in the INT116 trial. B, 5-year OS in Europe was 24% following surgery alone in the MAGIC trial. C, 5-year OS in Japan was 61% following surgery alone in the ACTS-GC trial. D, 5-year OS in Korea was 69% following surgery alone in the CLASSIC trial. These figures are used after modification of the original references[4–7]

FIGURE 2 Active chemotherapeutic agents for gastric cancer. Active agents for gastric cancer are classified into antimetabolite, platinum preparation, molecular-targeted therapy, topoisomerase inhibitor, taxane, and immune checkpoint inhibitor (ICIs). Red letters represent first-line chemotherapy regimens, blue letters represent second-line chemotherapy regimens, and green letters represent third-line singlet chemotherapy drugs. Bold letters represent currently available for oral medicines



the latter was pathologically confirmed as stage II/III with a negative cytology test[8]). As prognostic outcomes are geographically quite different, therapeutic strategies vary among countries. However, the most optimal therapeutic strategy, including chemotherapy for the specific clinical situation, should be selected based on the scientific evidence allowing for clinical benefits and toxicity profiles.

In this review, the history of development of chemotherapy for unresectable and/or recurrent advanced gastric cancer will be initially described. Then, perioperative adjuvant chemotherapy for resectable gastric cancer will be reviewed. Chemotherapy regimens included singlet, doublet, and triplet ones, including molecular targeted therapy as well as immune checkpoint inhibitors (ICIs).

2 | AGENTS ACTIVE FOR GASTRIC CANCER AND MECHANISM OF ACTION

In the history of gastric cancer chemotherapy, anti-metabolite (5-fluorouracil-5-FU) and platinum preparations (cisplatin-CDDP) as well as trastuzumab (HER2 neutralizing antibody, T-mab) and nivolumab (N-mab), an ICI, were critical and were adopted as first-line chemotherapy regimens for unresectable and/or recurrent gastric cancer worldwide (Figure 2, red color).

5-FU inhibits cytoplasmic thymidylate synthase (TS) activity to suppress thymine synthesis, followed by inhibition of DNA synthesis.[9] Levofolinate calcium (Leucovorin/LV) can also directly bind to TS to augment 5-FU activity,[10] and it is thus used as a part of the chemotherapeutic regimens such as FOLFOX[11,12] or FLOT.[13] Fluorinated pyrimidine preparations such as S1 (Taiho Pharmacoceutical Corp, Tokyo) and Xeloda (Roche Corp, France) represented by Capecitabine are available for oral delivery of 5-FU (Figure 2, bold).

S1 includes tegafur (5-FU derivative) with gimeracil and oteracil potassium to suppress its metabolic degradation in the liver and adverse events (AEs) in the gut, respectively,[14] whereas Xeloda includes capecitabine (5-FU prodrug activated by thymidine phosphorylase specifically overexpressed in cancer cells).[15] As a result, the 5-FU concentration in the blood with the use of Xeloda is theoretically lower while obtaining similar anti-tumor effects in comparison to S1.

Platinum preparations can be covalently cross-linked with adenine/guanine[16] to suppress DNA synthesis independently of 5-FU antagonism.[17] Thus, the combination regimen of 5-FU and platinum preparations has become the most popular first-line chemotherapy. Recently, CDDP is exchanged for oxaliplatin (OXP),[18] because CDDP is not convenient, requiring massive hydration to reduce renal toxicity.

In gastric cancer, first-line chemotherapy also included molecular targeted agents such as Trastuzumab (T-mab) in cases of HER2-positive gastric cancer.[19,20] HER2 oncogene (alternatively designated as ErbB2) is a membrane-bound tyrosine kinase expressed on cancer cells.

HER2 can form a heterodimeric complex with other ErbB family members such as HER1 (epidermal growth factor receptor-EGFR), HER3 (ErbB3), and HER4 (ErbB4), and their numerous cognate ligands (EGF, transforming growth factor-alpha, amphiregulin, betacellulin, heparin binding-EGF, epiregulin, neuregulin1-4) can transmit cancer cell proliferation signaling through cell surface receptors.[21]

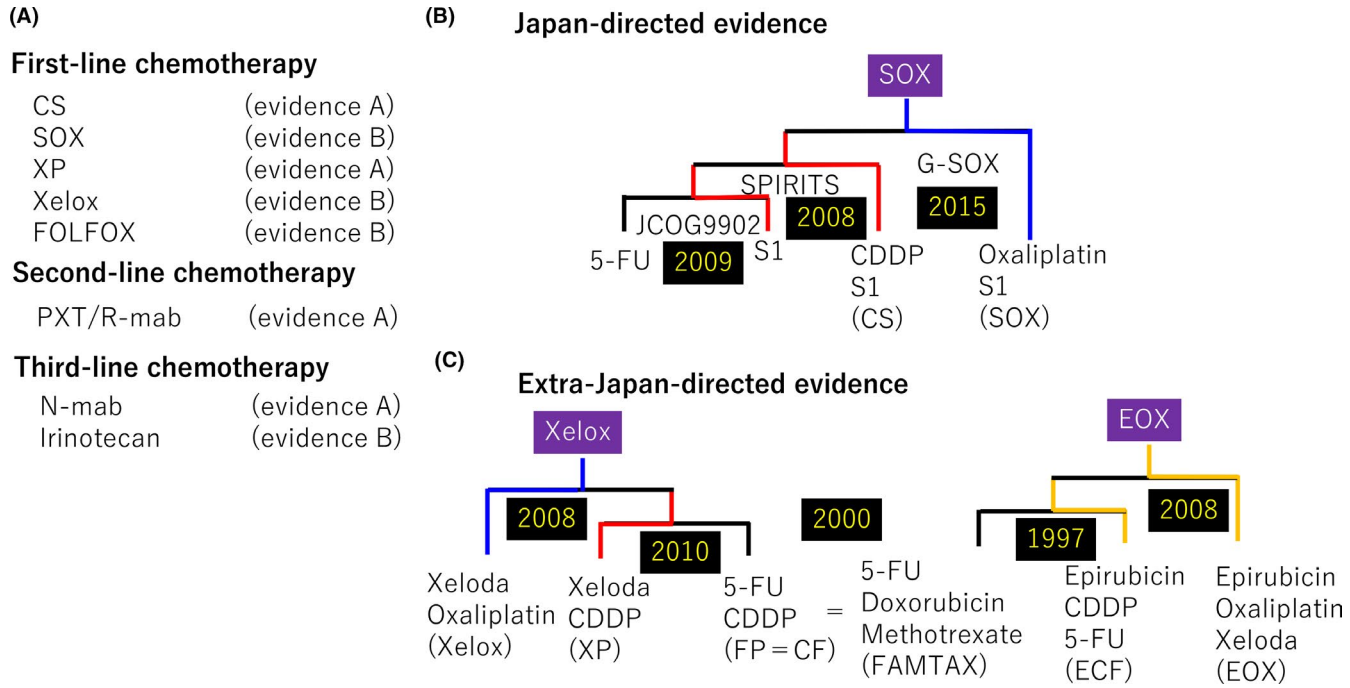


FIGURE 3 History and emerging chemotherapy regimens in first-line chemotherapy for unresectable and/or recurrent gastric cancer. A, The JGCA gastric cancer guidelines recommended chemotherapy regimens for first-line, second-line, and third-line chemotherapy in unresectable and/or recurrent gastric cancer. B, Japan-directed evidence in the JGCA gastric cancer guidelines at present recommend SOX as well as CS regimens. C, Extra-Japan-directed evidence in the JGCA gastric cancer guidelines at present recommends Xelox as well as XP, because epirubicine, which is used in Europe, is not available in Japan (yellow lines). Red colors represent level A evidence, and blue colors represent level B evidence in the JGCA gastric cancer guidelines. Publication years are shown in yellow letters in the black box

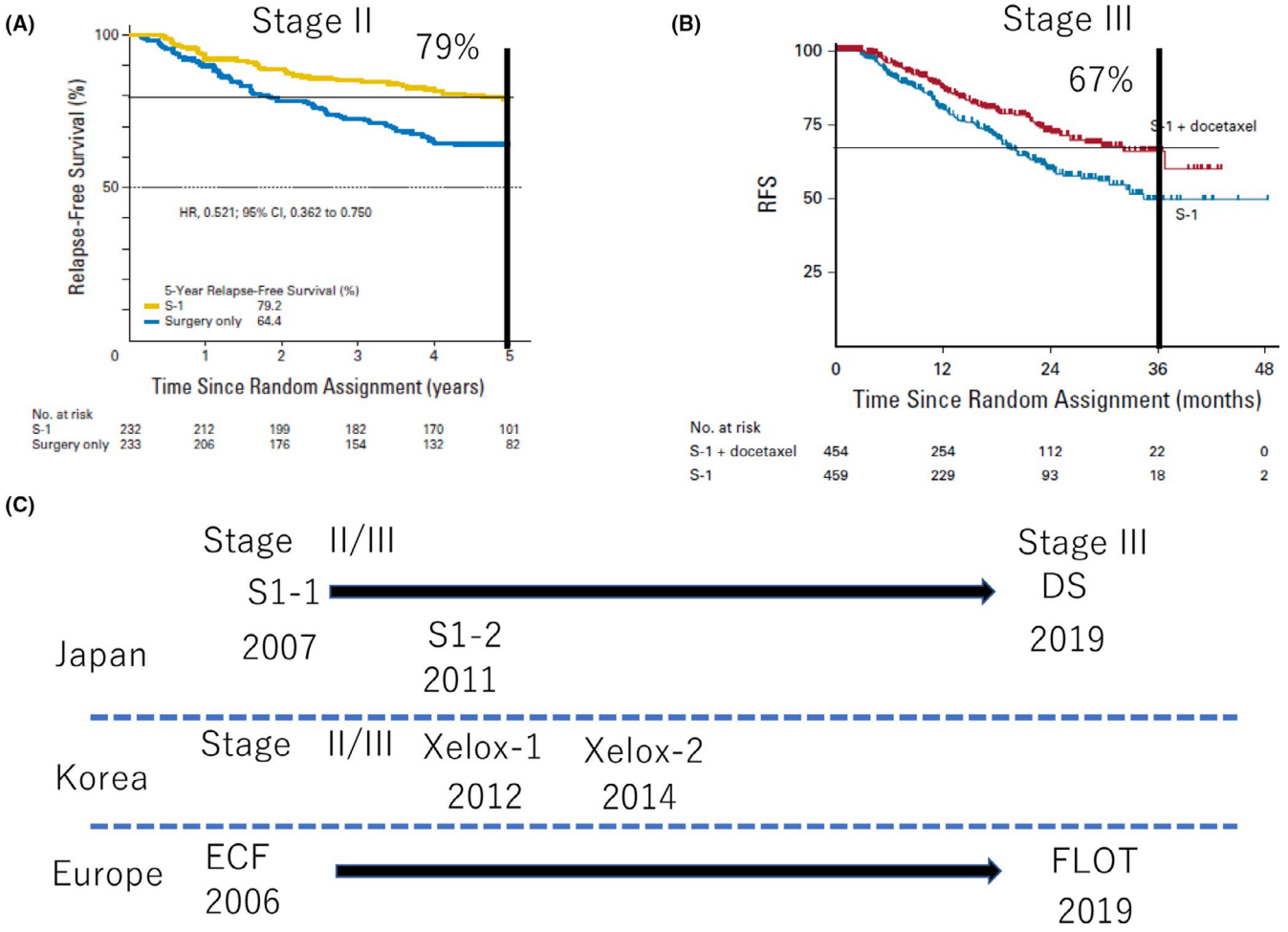


FIGURE 4 Recurrence-free survival (RFS) of resectable advanced gastric cancer following surgery plus postoperative adjuvant chemotherapy in phase III clinical trials. A, 5-year RFS was 79% in pathological stage II (the JGCA 13th edition) in the ACTS GC trial. B, 3-year RFS in pathological stage III was 67% following surgery alone in the JACCRO-GC7 trial. C, S1 adjuvant chemotherapy was initially shown to be effective in pathological stage II/III in 2007 (S1-1), and was re-analyzed with sufficient follow-up terms in 2011 (S1-2). CS adjuvant chemotherapy was shown to be superior to S1 adjuvant chemotherapy in 2019. Xelox adjuvant chemotherapy was initially shown to be effective in pathological stage II/III in 2012 (Xelox-1), and was re-analyzed with sufficient follow-up terms in 2014 (Xelox-2). These figures are used after modification of the original references[6,52]

Most intriguingly, HER2 DNA is frequently amplified in gastric cancer.[22,23] Thus, HER2 antagonism has therapeutic rationale in gastric cancer control.

For second-line chemotherapy, paclitaxel (PTX)/ramucirumab (R-mab) doublet regimen is effective in gastric cancer patients refractory to first-line chemotherapy (Figure 2, blue color).[24] PTX is a taxane that inhibits depolymerization of tubulin and subsequent cell division.[25] On the other hand, R-mab is a specific inhibitor of vascular endothelial growth factor (VEGF) receptor-2 (VEGFR2) expressed on the host cells.[26] Ligands of VEGFR2 are VEGF-A and VEGF-C/D derived from the tumor cells,[27] which are involved in angiogenesis and lymphangiogenesis,[28] respectively, to suppress tumor progression.

For third-line chemotherapy (Figure 2, green color), Nivolumab (N-mab) is effective in gastric cancer patients refractory to conventional chemotherapy.[29] N-mab theoretically antagonizes programmed death-1 (PD-1) expressed on stimulated T cells[30,31] and exhibits anti-tumor activity by modulating the host immune system against cancer cells.[32,33] Oral anticancer drug Lonsarf would be convenient for such compromised patients with drug resistance. Lonsarf is a combination of two agents: trifluridine, a nucleoside analog, and tipiracil, a thymidine phosphorylase inhibitor that prevents rapid metabolism of trifluridine.

3 | HISTORICAL SIGNIFICANCE OF FIRST-LINE CHEMOTHERAPY REGIMENS FOR HER2-POSITIVE UNRESECTABLE AND/OR RECURRENT GASTRIC CANCER

The Japanese Gastric Cancer Association (JGCA) gastric cancer treatment guidelines amended in 2018 (5th edition) clearly defined the recommended chemotherapy regimens for unresectable and/or recurrent gastric cancer (Figure 3A).[34]

The recommended chemotherapy regimens are composed of the following three categories: (a) regimens that had confirmed superiority over or non-inferiority to the conventional standard treatment in terms of OS in phase III clinical trials; (b) regimens demonstrating a reproducible clinical benefit in phase II clinical trial for a specific patient group; and (c) regimens that served as a control arm in multiple phase III clinical trials and were considered a standard treatment. The strength of evidence level is defined as A to D, and recommended treatments are composed of both evidence levels A and B.

For example, the ToGA trial[19,35] explored the efficacy for OS of T-mab (XPT regimen) in addition to the Xeloda/CDDP (XP) regimen, and XPT was demonstrated its prognostic efficacy in HER2-positive gastric cancer. On the other hand, the AVAGAST trial explored the efficacy and safety of T-mab in addition to XP in gastric cancer irrespective of HER2 status, where its efficacy for OS was not confirmed.[20] Both were phase III clinical trials, and the control regimen was the XP regimen as first-line standard chemotherapy for unresectable and/or recurrent gastric cancer. Hence, the XP regimen was considered an alternatively recommended first-line chemotherapy regimen (evidence A) in unresectable and/or recurrent gastric cancer.

In the ToGA trial, median OS of the XPT group was 13.8 months, whereas that of the XP group was 11.1 months ($P = .0046$),[19] and thus XPT was effective for OS improvement only in HER2-positive gastric cancer patients,[19,20] and the HER2 status must be initially examined for decision making.

S1/CDDP/T-mab (SPT) regimen also showed good prognosis (median OS were 16.0 and 14.6 months) in the two independent phase II clinical trials for HER2-positive gastric cancer,[36,37] and is thus considered as recommended first-line chemotherapy (evidence B) as well.

4 | FIRST-LINE CHEMOTHERAPY REGIMENS FOR HER2-NEGATIVE UNRESECTABLE AND/OR RECURRENT GASTRIC CANCER

In the JCOG9902 trial, S1 alone was non-inferior to 5-FU alone for OS in unresectable and/or recurrent gastric cancer,[38] and the SPIRITS trial confirmed superiority of the CS doublet regimen to S1 alone for OS.[39] Until recently in Japan, the CS regimen has long been considered the standard first-line chemotherapy, because no regimen is superior to the CS regimens for OS based on S1 oral medication at present (Figure 3B).

On the other hand, S1/OXP (SOX) exhibited non-inferiority to CS for progression-free survival (PFS) similarly to OS in the G-SOX trial.[18] In the JGCA gastric cancer treatment guideline, the SOX regimen was not level A, but level B, because non-inferiority of the SOX regimen for PFS was the primary endpoint in the G-SOX trial (Figure 3B). Nevertheless, the SOX regimen has become popular due to its convenient handling of AEs.

In Europe, the Epirubicin/CDDP/5-FU (ECF) regimen was demonstrated early to be superior to the 5-FU/Doxorubicin/Methotrexate (FAMTAX) regimen for OS in unresectable and/or recurrent gastric cancer,[40] where FAMTAX is considered to be equivalent to the CF regimen (Figure 3C).[41]

Afterwards, as OS was longer in the Epirubicin/OXP/Xeloda (EOX) group (median 11.2 months) than in the ECF group (median 9.9 months, $P = .02$) in the REAL2 trial,[42] the Xeloda/OXP (Xelox) combination is believed to be at least non-inferior to the CF combination in Epirubicin-based triplet multidrug regimens (Figure 3C).

In Korea, the XP regimen actually showed non-inferiority to the CF regimen for PFS of unresectable and/or recurrent gastric cancer,[43] and was used as control arms in the ToGA trial[19] and the AVAGAST trial[20] as previously described (evidence A)(Figure 3B). The Xeloda/OXP (Xelox) regimen is also approved as recommended first-line chemotherapy (evidence B) in the JGCA gastric cancer treatment guideline, allowing for the subset analysis of the REAL-2 trial.[42] Moreover, in the phase II NCT00985556 trial, both the SOX and Xelox regimens were equally active.[44]

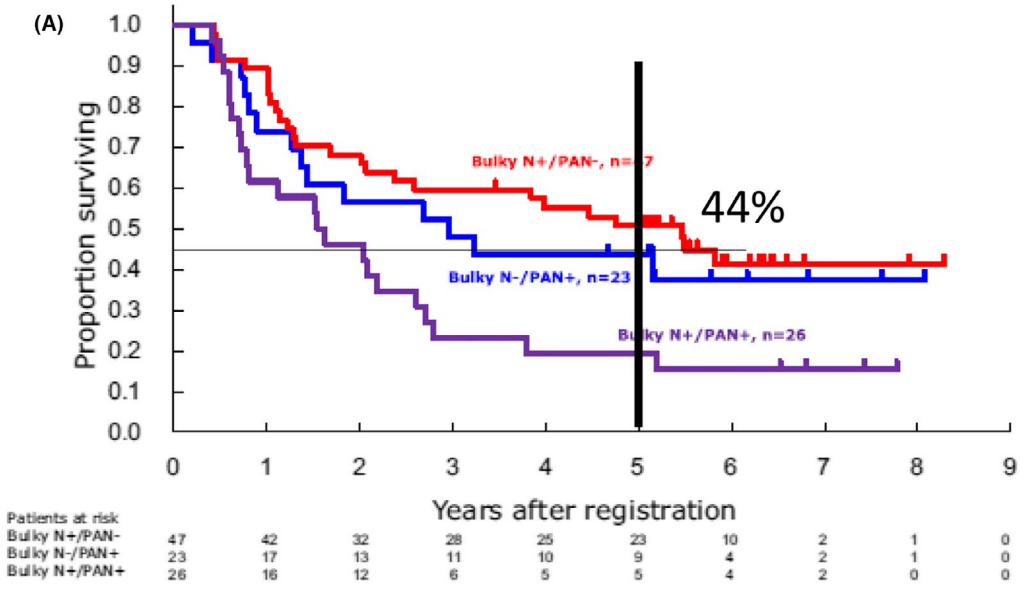
FOLFOX was also used for unresectable and/or recurrent gastric cancer as a control regimen of first-line chemotherapy in several phase III clinical trials,[45,46] and was additionally listed as a recommended regimen of first-line chemotherapy (evidence B).

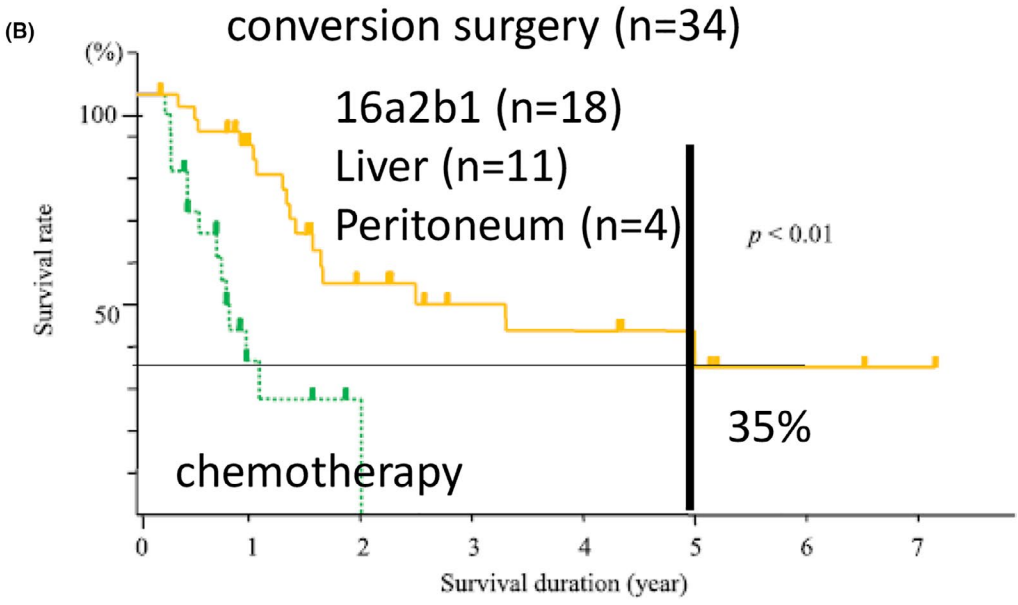
In the Checkmate-649 trial, recently, N-mab plus chemotherapy (CDDP-containing) clearly showed OS benefit as a first-line chemotherapy in comparison to chemotherapy alone irrespective of PD-L1 expression in HER2-negative unresectable and/or recurrent gastric cancer patients.[47] This result is also followed by the Attraction-4 trial, where N-mab in addition to the standard first-line chemotherapy (OXP-containing) prolonged PFS (10.5 months, $P = .0007$) in the interim analysis of the Attraction-4 phase II/III trial.[48] Thus, first-line chemotherapy will be changed in the near future.

5 | SECOND-LINE AND THIRD-LINE CHEMOTHERAPY

Second-line chemotherapy is administered to patients with treatment failure of first-line chemotherapy, and the RAINBOW trial demonstrated that the Paclitaxel/Ramucirumab (PTX/R-mab) regimen significantly increases OS in comparison with PTX alone[24] (Figure 3A). Interestingly, The Cancer Genome Atlas (TCGA) molecular profile revealed frequent genomic amplification of VEGF as well as HER2 in chromosomal instable (CIN) gastric[22] and esophageal adenocarcinoma.[23] However, the relationship between the VEGF status and clinical efficacy of the PTX/R-mab regimen remains elusive at present, and its use is not conditional differently from T-mab, putatively because its target host cells include vascular and lymphatic endothelial cells.

The recommended third-line chemotherapy includes singlet agents such as N-mab or Irinotecan (Figure 3A). In the ATTRACTION-2 trial, N-mab, an ICI, drastically improves OS in comparison to best supportive care (BSC) in advanced gastric cancer that is refractory to chemotherapy.[29] The TAGS trial also demonstrated


(A)
Proportion surviving
Bulky N+/PAN-, n=47
Bulky N-/PAN+, n=23
Bulky N+/PAN+, n=26
44%
Years after registration
Patients at risk
Bulky N+/PAN- 47 42 32 28 25 23 10 2 1 0
Bulky N-/PAN+ 23 17 13 11 10 9 4 2 1 0
Bulky N+/PAN+ 26 16 12 6 5 5 4 2 0 0


(B)
conversion surgery (n=34)
16a2b1 (n=18)
Liver (n=11)
Peritoneum (n=4)
p < 0.01
35%
chemotherapy
Survival rate
Survival duration (year)

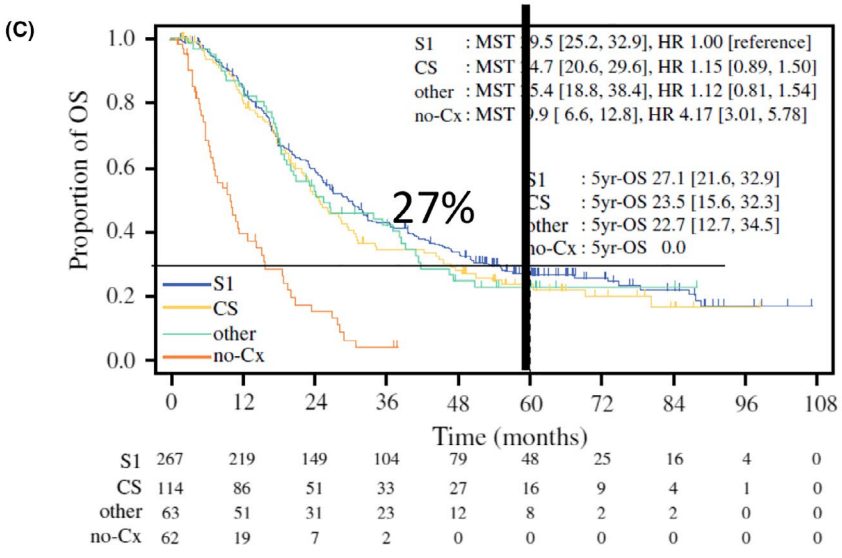

(C)
S1 : MST 29.5 [25.2, 32.9], HR 1.00 [reference]
CS : MST 24.7 [20.6, 29.6], HR 1.15 [0.89, 1.50]
other : MST 25.4 [18.8, 38.4], HR 1.12 [0.81, 1.54]
no-Cx : MST 9.9 [6.6, 12.8], HR 4.17 [3.01, 5.78]
S1 : 5yr-OS 27.1 [21.6, 32.9]
CS : 5yr-OS 23.5 [15.6, 32.3]
other : 5yr-OS 22.7 [12.7, 34.5]
no-Cx : 5yr-OS 0.0
27%
Proportion of OS
Time (months)
S1 267 219 149 104 79 48 25 16 4 0
CS 114 86 51 33 27 16 9 4 1 0
other 63 51 31 23 12 8 2 2 0 0
no-Cx 62 19 7 2 0 0 0 0 0 0

FIGURE 5 OS of stage IV gastric cancer following surgery plus chemotherapy. A, 5-year OS was 44% in patients with advanced gastric cancer with paraaortic lymph node (PAN) metastasis alone (blue line) who underwent irinotecan/CDDP or CS neoadjuvant chemotherapy followed by gastrectomy with D3 lymph node dissection in the JCOG0001 and JCOG0405 trials, respectively. B, 5-year OS was 35% in patients with stage IV gastric cancer (yellow line) who underwent DCS neoadjuvant chemotherapy followed by gastrectomy in the National Cancer Center East Hospital, where stage IV gastric cancer included 18 patients with PAN metastasis.[11] C, Patients with gastric cancer with CY1 and/or P1a who underwent gastrectomy with postoperative chemotherapy such as S1 (blue), CS (yellow), and other chemotherapeutic regimens (green) showed 5-y OS of 27%, 24%, and 23%, respectively, in contrast to no chemotherapy group (~0%). These figures are used after modification of the original references[63,64,66]

that Lonsarf, an oral anticancer drug, alone can improve OS in comparison with BSC in the third-line chemotherapy setting.[49]

T-mab Deruxtecan (DS-8201a) is an antibody-drug conjugate (ADC) consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and cytotoxic topoisomerase inhibitor exatecan mesylate. In the DECTINY-Gastric01 trial, DS-8201a led to significant improvements in response and OS, as compared with conventional therapies, among patients with HER2-positive gastric cancer that had progressed while they were receiving at least two previous therapies (as third-line chemotherapy), including T-mab.[50] For DS-8201a, myelosuppression and interstitial lung disease were the notable toxic effects.

6 | POSTOPERATIVE ADJUVANT CHEMOTHERAPY FOR RESECTABLE GASTRIC CANCER

Adjuvant chemotherapy development has differed greatly between countries; however, it is associated with first-line chemotherapy regimen (Figure 1A-D). In Japan, postoperative 1-year S1 adjuvant chemotherapy was confirmed to improve OS in comparison to surgery alone in pathological stage II/III gastric cancer[8] (Figure 4C, see S1-1).

Postoperative 1-year S1 adjuvant chemotherapy showed better RFS than surgery alone (Figure 1C), especially in pathological stage II.[6] The 5-year RFS rate of the pathological stage II gastric cancer patients was 79.2% in the S1 group and 64.4% in the surgery alone group (Figure 4A).

Postoperative half-year S1 adjuvant chemotherapy was then compared to the standard 1-year S1 administration in stage II gastric cancer, and the half-year S1 chemotherapy did not demonstrate non-inferiority to the standard 1-year chemotherapy.[51] Thus, long-term 1-year chemotherapy is strongly recommended in stage II gastric cancer.

On the other hand, in the JACCRO GC-7 trial, in pathological stage III gastric cancer, postoperative Docetaxel (DTX)/S1 (DS) regimen increased RFS in comparison to the 1-year standard adjuvant S1 chemotherapy,[52] the success of which is associated with that in first-line chemotherapy.[53] The 3-year RFS rate of pathological stage III gastric cancer patients was 67% in the DS group and 50% in the S1 group (Figure 4B).

In Korea, a half-year doublet postoperative chemotherapy (Xelox) improved disease-free survival (DFS) in comparison to surgery alone[19] (Figure 4C, see Xelox-1), and long-term follow-up recapitulated the initial analysis of prognosis,[7] as in the AGTS-GC trial.

Direct comparison between S1-based regimen and Xeloda-based regimen was defective, and thus which regimen is better for pathological stage II/III gastric cancer is yet to be established. Anyway, postoperative adjuvant chemotherapy regimens for pathological stage II/III gastric cancer are available for S1, DS, and Xelox at present.

In ARTIST2 trial, the most recent postoperative adjuvant SOX or SOX radiotherapy (SOXRT) was proved to be effective in prolonging DFS, when compared to S1 monotherapy in patients with curatively D2-resected, stage II/III gastric cancer.[54]

7 | NEOADJUVANT CHEMOTHERAPY FOR RESECTABLE GASTRIC CANCER

In European countries, the ECF regimen for perioperative chemotherapy was demonstrated to improve OS in comparison to surgery alone in resectable advanced gastric cancer (Figure 1B).[5] The 5-year OS with perioperative chemotherapy plus surgery was 37%, which is a 13% improvement over that with surgery alone. Perioperative chemotherapy includes preoperative chemotherapy designated as neoadjuvant chemotherapy, which was considered to be a promising strategy for aggressive gastric cancer.

Because the prognosis of resectable advanced gastric cancer without adjuvant therapy between Western and Eastern counties is so different (~30% and ~70% for 5-year OS, respectively), in Japan, neoadjuvant chemotherapy is limited to clinically aggressive gastric cancer.

JCOG0001 and JCOG0405 showed promising efficacy of CS neoadjuvant chemotherapy for gastric cancer with extensive lymph node metastasis, which included both curable stage (bulky lymph node disease in the regional lymph nodes) as well as paraaortic lymph node metastasis (stage IV). Hence, the recent gastric cancer treatment guideline described that neoadjuvant chemotherapy is weakly recommended for this special disease.

In the JCOG0501 trial, on the other hand, additional neoadjuvant chemotherapy with the CS regimen was compared only in macroscopically aggressive gastric cancer (type IV and giant type III) patients who received standard 1-year postoperative S1 chemotherapy[55]; however, no prognostic improvement was seen in the additional neoadjuvant group.[56] At present, in Japan, neoadjuvant therapy is considered to be limited to specific gastric cancer and can

be largely performed only in clinical studies. The SOX regimen in the neoadjuvant setting is also being tested in advanced gastric cancer with cT3-4N1-3 in the JCOG1509 (NAGISA) trial.

Recently, in the RESOLVE trial in China, perioperative SOX improved 3-year DFS compared with postoperative XELOX ($P = .045$), whereas postoperative SOX was non-inferior to postoperative Xelox in gastric or gastro-esophageal junction adenocarcinoma patients with cT4a/N + M0 or cT4bNxM0.[57] These findings suggested that perioperative SOX is effective in the specific advanced gastric cancer even in Eastern countries.

The novel Docetaxel/Oxaliplatin/S1 (DOS) neoadjuvant chemotherapy is being challenged in recent clinical trials in Eastern countries for resectable gastric cancer (PRODIGY trial),[58] gastric cancer with extensive nodal metastasis,[59] and esophagogastric cancer.[60] In the PRODIGY trial, addition of neoadjuvant DOS to D2 gastrectomy and postoperative adjuvant S1 chemotherapy led to significant tumor downstaging and improved PFS with acceptable safety,[61] and this treatment strategy is also promising as a treatment option for resectable advanaced gastric cancer.

In Western countries, perioperative chemotherapy has progressed outstandingly as shown in the FLOT4 trial,[13] in which the perioperative 5-FU/LV/OXP/DTX (FLOT) chemotherapy improved OS (5-year OS of 45%) in comparison to ECF/EOX (the standard perioperative chemotherapy)(5-year OS of 36%). The FLOT regimen is corresponding to the DOS regimen developing in Eastern countries. Development of novel successful adjuvant chemotherapy took over 10 years in both Eastern and Western countries (Figure 4C).

8 | CHEMOTHERAPEUTIC STRATEGIES FOR STAGE IV GASTRIC CANCER

Even in stage IV gastric cancer, surgery has become promising for a cure along with recently emerging therapeutic strategies such as neoadjuvant chemotherapy or conversion surgery.

For the first time, in the JCOG0405 trial, stage IV gastric cancer with paraaortic lymph node metastasis can be cured with neoadjuvant chemotherapy of the CS regimen (two or three courses) followed by surgery.[62] The 5-year OS was 43.5% in gastric cancer patients with regional bulky N (−)/PAND (+) who underwent D2 + paraaortic lymph node dissection[63] (Figure 5A).

On the other hand, potent chemotherapy followed by conversion surgery also recently produced a cure for stage IV gastric cancer that included paraaortic lymph node metastasis; conversion surgery after DCS chemotherapy produced 5-year OS of over 30%-40% in stage IV gastric cancer[64,65] (Figure 5B). As almost all cases of conversion surgery can be done after first-line chemotherapy, emerging new first-line chemotherapy is greatly anticipated to increase the chance for conversion surgery followed by a cure in the future.

For peritoneal disease of gastric cancer, postoperative chemotherapy after gastrectomy that leaves no macroscopically visible disease has survival benefits for gastric cancer patients with CY1 and/or P1a,[66] where patients who received any chemotherapy showed 5-year OS of 20%-30%, and those who received no chemotherapy exhibited 5-year OS below 10% (Figure 5C).

9 | FUTURE PROSPECTIVE BASED ON GENOMIC CLASSIFICATION OF GASTRIC CANCER

Gastric cancer was classified by TCGA (The Cancer Genome Atlas) into molecular profiles including Epstein-Barr virus (EBV)-integrated gastric cancer, microsatellite instability-high (MSH-H) gastric cancer, chromosomally instable (CIN) gastric cancer, and genomic stable (GS) gastric cancer.[22]

Both EBV and MSI-H gastric cancers are uniquely characterized by epigenetic carcinogenesis (gene silencing of p16 and MLH1, respectively, mainly by gene promoter DNA cytosine methylation).[22] N-mab is recommended for EBV-positive gastric cancer and MSI-H gastric cancer, because both subtypes demonstrated PD-L1 + immune cells with tumor-infiltrating patterns.[67]

Recent genomic profiles also revealed that unique ARID1A mutations are frequently found in both EBV and MSI-H gastric cancer,[68] and such tumors with ARID1A mutations are highly sensitive to glutathione inhibition because of altered metabolism of cysteine via synthetic lethality mechanism.[69]

On the other hand, almost all CIN gastric cancers harbor TP53 mutation with intestinal type histology. TP53 mutation leads to inactivation of tumor suppressive function as well as gain of function (GOF),[70,71] which could be molecularly targeted because mutated TP53 protein is overexpressed in human cancers. Mutated TP53 can bind specifically with TP63 and many other onco-proteins, gaining an oncogenic potential, and CIN gastric cancer is considered to be addicted to TP53 GOF.[72]

Recently, the number of patients with TP53 mutations in metastatic tumors was demonstrated to be significantly higher among those with liver metastasis (87%) in contrast to those without liver metastasis (40%), and moreover TP53 mutations in metastatic liver tumors and corresponding primary tumors were almost identical in 97% of cases.[73] These data suggested that TP53 mutations could be outstanding molecular targets in CIN gastric cancer.

GS gastric cancer is characterized by diffuse-type gastric cancer,[22] which is characterized by emerging peritoneal disease.[74] However, even the most powerful intraperitoneal/intravenous chemotherapy does not produce satisfactory clinical outcomes.[75] Diffuse-type gastric cancer is characterized by CDH1/RhoA mutations and is addicted to RhoA signal.[76,77] In the new era of gastric cancer clinics, specific molecular target would be promising based on the genome classification above.

In conclusion, history and emerging trends in chemotherapy for gastric cancer have been reviewed. Conventional anticancer drugs non-specifically suppressed DNA synthesis and/or cell division, whereas emerging therapeutic trends included molecular-targeted as well as immune-targeted therapy, which is well consistent with molecular profiles.[22,23] Thus, further deep understanding of the

genetic profiles in gastric cancer will expand novel therapeutic strategies in the near future.

CONFLICT OF INTEREST

There is no conflict of interest in this article.

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